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Endotoxic Shock After Long-Term Resuscitation of Hemorrhage/ Reperfusion Injury Decreased Splanchnic Blood Flow and Eicosanoid Release

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Objective

The authors examine the hypothesis that hemorrhage/reperfusion injury predisposes the splanchnic bed to decreased prostacyclin (PGI_2) release and blood flow after subsequent endotoxin challenge.

Summary Background Data

Prostacyclin is a potent vasodilator that has been demonstrated to be an important regulator of splanchnic blood flow. Previous studies have demonstrated that during resuscitation from severe hemorrhage, there is a marked reduction in intestinal PGI_2 levels, which is associated with reduced splanchnic perfusion.

Methods

Anesthetized Sprague-Dawley rats underwent hemorrhage to a mean arterial pressure of 30 mmHg for 30 minutes followed by the reinfusion of shed blood. Then the animals were maintained on total parenteral nutrition (TPN) for 10 days, after which time they received 20 mg/kg *Escherichia coli* endotoxin intraperitoneally. Aortic and superior mesenteric artery (SMA) blood flow was monitored with a Doppler flow probe. The splanchnic bed was excised and perfused *in vitro* for measurement of venous effluent eicosanoid concentrations. Controls consisted of animals that received TPN and endotoxin but did not undergo hemorrhage and resuscitation (sham).

Results

Total parenteral nutrition support of sham animals followed by endotoxin challenge did not alter splanchnic eicosanoid release or blood flow. Hemorrhage/reperfusion animals supported by long-term TPN and challenged with endotoxin demonstrated a threefold decrease in splanchnic prostacyclin metabolite (6-keto-$PGF_{1\alpha}$) release and a 50% decrease in SMA blood flow.

Conclusions

Hemorrhage/reperfusion injury predisposes the splanchnic bed from rats sustained with long-term TPN to decreased release of PGI_2 and SMA blood flow when challenged with endotoxin as a second injury.

Eicosanoids have been shown to contribute to the regulation of splanchnic blood flow.[1-4] Prostacyclin (PGI_2), a potent endogenous vasodilator, has been shown to be the major arachidonic acid metabolite synthesized and released by the splanchnic bed. Loss of endogenous splanchnic PGI_2 after acute hemorrhage/reperfusion injury was shown to contribute to both decreased splanchnic release of PGI_2 and to decreased splanchnic blood flow.[5-8]

Circulatory shock as a result of bacterial sepsis continues to be a serious clinical problem, exposing patients to significant mortality and morbidity.[9-11] The release of endotoxin by gram-negative bacteria has been shown to one of the most important factors that contributes to organ failure (kidney, intestine, heart, etc.) and the metabolic derangements described during bacterial sepsis.[12] The effect of bacterial endotoxin on the release of a large number of humoral mediators, including eicosanoids, have been examined in many animal models.[9] There are no current data available describing the effects of endotoxin, administered as a second injury, to animals treated with long-term nutritional support after an initial injury of acute hemorrhage/reperfusion on endogenous splanchnic eicosanoid release and splanchnic blood flow. The current study uses a model of acute hemorrhage/reperfusion injury followed by 10 days of nutritional support with total parenteral nutrition (TPN), and a subsequent challenge with intraperitoneal *Escherichia coli* endotoxin, to more closely mimic clinical patients developing sepsis after an initial hemorrhage/reperfusion injury. This animal model will be used to examine the hypothesis that hemorrhage/reperfusion injury predisposes the splanchnic bed to decreased eicosanoid release and decreased splanchnic blood flow when challenged with endotoxin as a second injury.

METHODS

Shock Model

The shock rat model was prepared as described previously.[5-7] Sprague-Dawley rats (300–350 g) were housed in the animal care facility of Dallas Veterans Medical Center and were used in compliance with regulations of the University of Texas Southwestern Medical School and the Dallas Veterans Affairs Medical Center. The animal studies were conducted according to protocols reviewed and approved by the Institutional Animal Care and Use Committee and adhered to the guidelines promulgated by the National Institutes of Health. All animals were maintained on normal rat chow and allowed water *ad libitum.* The rats were weighed and anesthetized with metafane. Each animal received 50 units of heparin intravenously, and the right femoral artery was cannulated with a PE-50 polyethylene cannula and interfaced to Grass recorder for constant monitoring of the blood pressure. Group 1 animals underwent femoral artery cannulation without hemorrhage and placement of TPN cannulas, and were supported for 10 days of TPN, given carrier (no *E. coli* endotoxin), and are termed the sham group. Group 2 animals (sham group + lipopolysaccharide [LPS]) had femoral artery cannulas, TPN cannulas placed, were not subjected to hemorrhage/reperfusion, were treated with TPN for 10 days, and were subjected to *E. coli* endotoxin. Group 3 animals were subjected to acute hemorrhage to 30 mm of mercury for 30 minutes followed by blood reperfusion and stabilized at preshock arterial pressure for 60 minutes followed by TPN treatment for 10 days, subjected to *E. coli* endotoxin, and are termed the SK + R + LPS group. The amount of blood removed for hemorrhage was 9 ± 0.3 mL, and an additional 1 ± 0.1 mL was removed approximately each 10 minutes to maintain the level of hemorrhage. All shed blood was returned during the period of reperfusion and arterial pressure was well maintained at prehemorrhage levels and was similar to values previously reported by our laboratory.[5-7] The *E. coli* endotoxin was given 20 mg/kg i.p. to group II and group III animals (carrier alone to group I), and after 5 hours, the animals underwent laparotomy.

Total Parenteral Nutrition Preparation

Male Sprague-Dawley rats in the sham and SK + R groups were treated with TPN, as described previously.[13-15] The rats were housed in metabolic cages in a room with regulated temperature, humidity, and light/dark cycles. The rats were fed standard rat chow and water *ad libitum* during a stabilization period of 4 days. A central venous line made from silicon tubing (Silastic, ID 0.020 inches, Dow Corning, Midland, MI) was placed through the right internal jugular vein and advanced into a central venous position. The distal end of the tube was tunneled subcutaneously to the nape of the neck, where it exited the skin. A 14-gauge over the needle intravenous catheter was inserted in the nape of the neck and advanced in a caudal direction in the subcutaneous layer. This line was placed in a spring coil apparatus, secured to a harness, and connected to a dual swivel mechanism. This arrangement allowed the animals to move freely throughout their cages. After sham or hemorrhage/reperfusion, the animals were maintained on a high calo-

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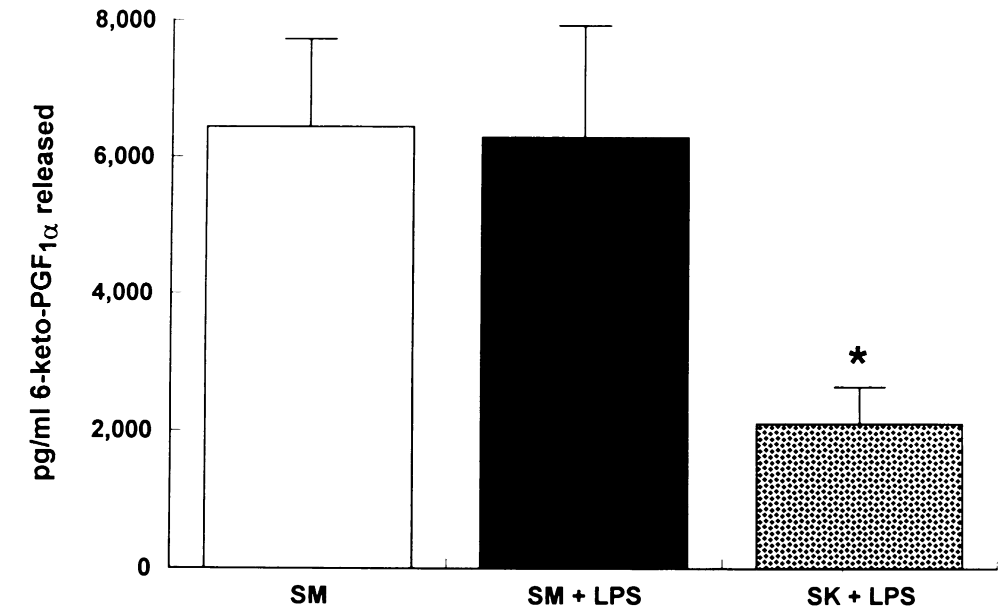

Figure 1. The effect of hemorrhage/reperfusion and total parenteral nutrition (TPN) for 10 days followed by endotoxin challenge on *in vitro* 6-keto-PGF$_{1\alpha}$ release in the rat. Male rats were subjected to acute hemorrhage to 30 mmHg for 30 minutes, resuscitated with shed blood, and then maintained on TPN for 10 days (SK + R group, filled box) and compared with sham-operated controls (open box, instrumented and maintained on TPN for 10 days but nonshocked, stippled box, instrumented and maintained on TPN for 10 days, treated with endotoxin but nonshocked). After 10 days, the SK + R rats (filled box) and half the sham rats (stippled box) were treated with *E. coli* endotoxin (lipopolysaccharide [LPS], 20 mg/kg, i.p.) and 5 hours later underwent laparotomy. The splanchnic bed was perfused *in vitro* Krebs-Henseleit buffer at 3 mL/minute. Basal release of 6-keto-PGF$_{1\alpha}$ (PGI_2 metabolite) was measured by EIA at 15 minutes of perfusion. Data are presented as pg 6-keto-PGF$_{1\alpha}$ released/mL (mean ± standard error of the mean, *significance compared to sham and sham + LPS $p < 0.01$ level by analysis of variance, N = 6 or more).

ric, protein-rich infusate (50% dextrose, 8.5% Travasol (Travasol Laboratories).[13-15]

Preparation of *In Vivo* Superior Mesenteric Artery and Aortic Blood Flow Studies

Following laparotomy, superior mesenteric artery (SMA) and abdominal aortic blood flow was measured using mean transmittable Doppler flowmeters (Models 1RB109 and 2SB73, Transonic Systems, Ithaca New York) as described by Myers,[5] Bailey,[16] Drost,[17] and Cristol.[18] Blood flow measurements were recorded for 60 minutes, before removal and cannulation of the SMA for *in vitro* perfusion experiments. The SMA blood flow data are reported as a percent of the aortic blood flow.

Preparation of *In Vitro* Splanchnic Bed Perfusion Experiments

After the *in vivo* SMA and aortic blood flow measurements, the SMA was cannulated rapidly with PE-50 tubing and removed with the intact intestine. The cannulated splanchnic bed was placed in a warming jacket and perfused *in vitro* with Krebs-Henseleit buffer (O_2/CO_2 95:5, pO_2 460 ± 10 mmHg) at 3 mL/minute.[4-6,8] Basal renal venous effluent was collected after 15 minutes of perfusion. Enzyme immunoassays (EIAs) for prostacyclin metabolite (6-keto-PGF$_{1\alpha}$ [PGI_2 metabolite]) and thromboxane B_2 (TxB_2, metabolite of thromboxane A2) and were performed within a 2-week period. Indomethacin was used to confirm specificity of the EIAs. Eicosanoid data are reported as ng eicosanoid released/minute of venous effluent collection.

Enzyme Immunoassays

The EIA for 6-keto-PGF$_{1\alpha}$ (prostacyclin metabolite) and TxB_2 were performed on Krebs-Henseleit buffer. The EIA reagents were purchased from Cayman Chemical (Ann Arbor, Michigan).[15,19] Data are expressed as pg prostanoid released/mL protein (stimulated − the basal; mean ± standard error of the mean).

Statistical Analyses

All data are reported as mean ± standard error of the mean, and six animals were used in all sham and experimental groups. All data were assessed by analysis of variance. Results were considered significant when $p < 0.05$. *Post hoc* multiple comparisons were made using a Bonferroni strategy at the 0.05 level.

RESULTS

All animals subjected to hemorrhage/reperfusion and sham operation survived after 10 days of TPN. The *in vitro* perfused sham animals (group I) released 6-keto-PGF$_{1\alpha}$ as the major arachidonic acid metabolite and was sixfold higher than thromboxane B_2 (Figs. 1 and 2). Treatment of the sham + TPN animals with endotoxin

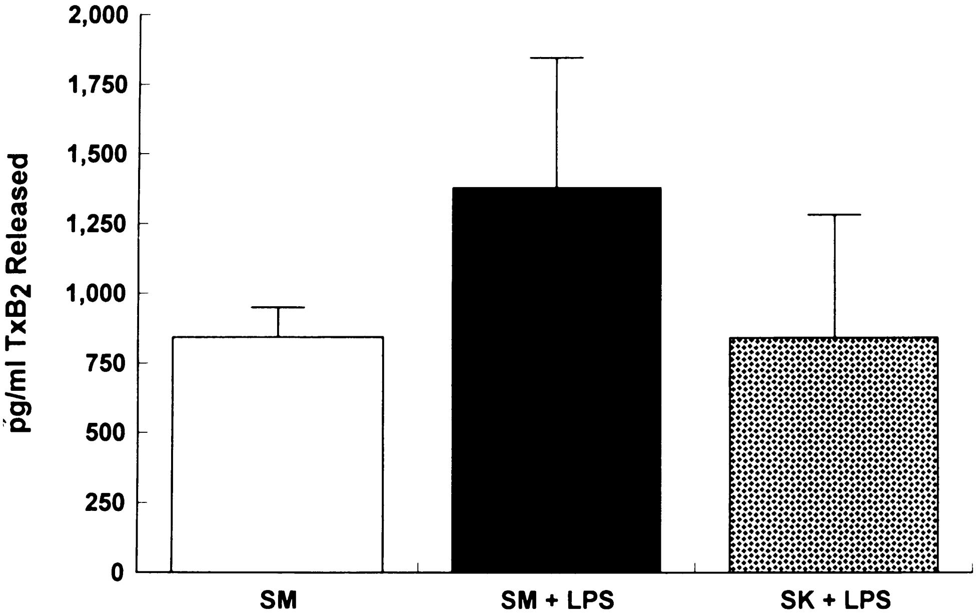

Figure 2. The effect of hemorrhage/reperfusion and total parenteral nutrition (TPN) for 10 days followed by endotoxin challenge on *in vitro* thromboxane B_2 release in the rat. Male rats were subjected to acute hemorrhage to 30 mmHg for 30 minutes, resuscitated with shed blood, and then maintained on TPN for 10 days (SK + R group, filled box) and compared with sham-operated controls (open box, instrumented, and maintained on TPN for 10 days but nonshocked, stippled box, instrumented, and maintained on TPN for 10 days, treated with endotoxin but nonshocked). After 10 days, the SK + R rats (filled box) and half the sham rats (stippled box) were treated with *E. coli* endotoxin (lipopolysaccharide[LPS], 20 mg/kg, i.p.) and 5 hours later underwent laparotomy. The splanchnic bed was perfused *in vitro* Krebs-Henseleit buffer at 3 mL/minute. Basal release of thromboxane B_2 (thromboxane A_2 metabolite, TxB_2) was measured by EIA at 15 minutes of perfusion. Data are presented as pg TxB_2 released/mL (mean ± standard error of the mean, *significance compared with sham and sham + LPS $p < 0.01$ level by analysis of variance, N = 6 or more).

did not alter splanchnic release of 6-keto-$PGF_{1\alpha}$ but did increase endogenous TxB_2 release, although this increase did not reach statistical significance (Figs. 1 and 2). Subjecting the sham animals supported by 10 days of TPN to endotoxin did not alter the ratio of SMA/aortic blood flow compared with the sham animals not treated with endotoxin (Fig. 3).

Subjecting the animals to hemorrhage/reperfusion followed by 10 days of TPN and secondary endotoxin challenge decreased endogenous splanchnic release of 6-keto-$PGF_{1\alpha}$ by 70% but did not alter release of TxB_2 (Figs. 1 and 2). Subjecting the hemorrhage/reperfusion animals supported for 10 days by TPN to endotoxin caused a profound decrease in the ration of SMA/aortic blood flow compared with the sham and sham + LPS groups (Fig. 3).

DISCUSSION

Circulatory shock as a result of bacterial sepsis continues to be a serious clinical problem, exposing patients to significant mortality and morbidity.[9-11] The release of endotoxin by gram-negative bacteria has been shown to be one of the most important factors that contributes to organ failure (kidney, intestine, heart, etc.) and the metabolic derangements described during bacterial sepsis.[1-4,12] The effect of bacterial endotoxin on the release of a large number of humoral mediators, including eicosanoids, have been examined in many animal models.[9]

Eicosanoids have been implicated as one class of vasoactive compounds that contribute to the pathophysiologic alterations noted during various injury models, including endotoxic shock.[20-25] Previous studies have shown that endotoxemia was associated with increased plasma levels of both vasoconstrictor and vasodilator eicosanoids.[20-22,24,25] The vasoconstrictor eicosanoids found in the plasma during endotoxemia include TxB_2, $PGF_{2\alpha}$ and leukotriene D_4. The vasodilator eicosanoids found in the plasma during endotoxemia include PGI_2 (6-keto-$PGF_{1\alpha}$) and prostaglandin E_2. Although the opposing actions and interactions of these eicosanoids are complex, their net effect in contributing to mortality after endotoxin administration has been reported to be significant. For the most part, these studies showed that specific inhibition of TxB_2 was associated with improved survival, implicating TxB_2 as a pathogenic factor in endotoxin-induced shock.[15,20] One must be aware that other authors have shown that inhibition of the conversion of arachidonic acid to prostanoids, as well as thromboxane, was associated with improved animal survival. These findings describe an important weakness inherent to examining serum eicosanoid levels during injury models, that the specific visceral organ(s) responsible for these changes cannot be identified.

Eicosanoids have been shown to have both potent vasodilator and vasoconstrictor actions in the splanchnic vascular bed. The major vasodilators are PGI_2 and prostaglandin E_2, and the major vasoconstrictors are leukotriene C_4 and Thromboxane A_2 (TxA_2).[26-29] Eicosanoids

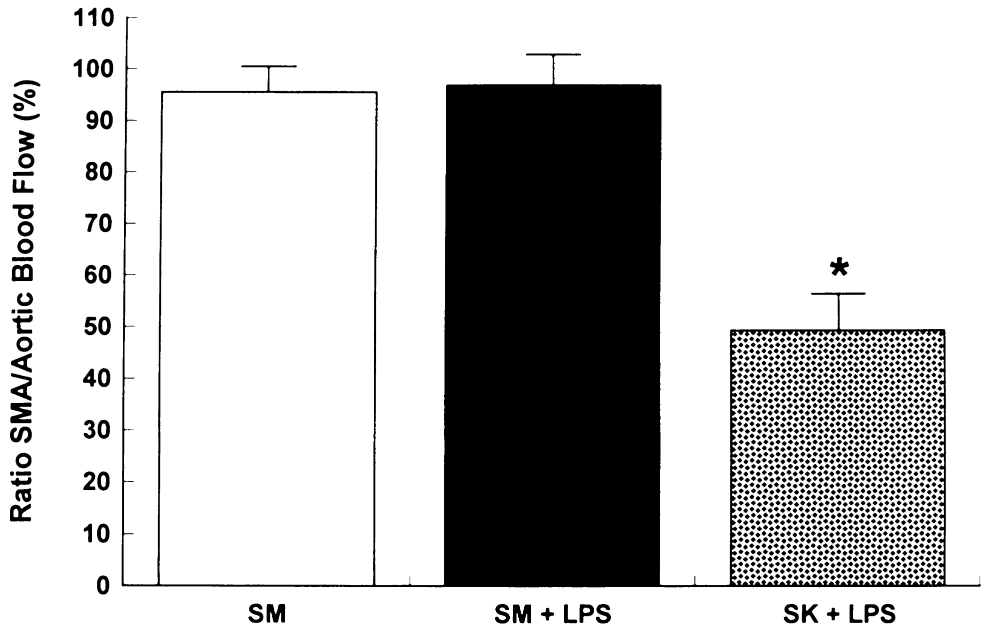

Figure 3. The effect of hemorrhage/reperfusion injury and 10 days of total parenteral nutrition (TPN) on superior mesenteric artery (SMA) and aortic blood flow. Male rats were subjected to acute hemorrhage to 30 mmHg for 30 minutes, resuscitated with shed blood, and then maintained on TPN for 10 days (SK + R group, filled box) and compared with sham-operated controls (open box, instrumented and maintained on TPN for 10 days but nonshocked) and sham controls treated with endotoxin (stippled box, instrumented and maintained on TPN for 10 days, treated with endotoxin but nonshocked). The SK + R and half the sham animals were anesthetized and treated with *E. coli* endotoxin (lipopolysaccharide [LPS], 20 mg/kg, i.p.), and underwent laparotomy 5 hours later. Superior mesenteric artery and abdominal aortic blood flow were measured in sham, sham and SK + R rats before removal of the splanchnic bed and *in vitro* perfusion, as described under Methods. Data are recorded as mL/minute and reported as SMA blood flow as a percent of aortic blood flow (mean ± standard error of the mean, N = 6). *significant compared with sham and sham + LPS group at $p < 0.05$ by Student's t test.

have been shown to be synthesized by the entire gastrointestinal tract.[30] Thus, the entire gastrointestinal tract could serve as a source for locally vasoactive eicosanoids. Eicosanoid synthesis in the resting intestine favored the vasodilator eicosanoids as cyclooxygenase inhibition decreased blood flow to the intestine.[28,29] The importance of resting intestinal vasodilator eicosanoids was further shown by experiments using exogenous TxA_2 to constrict the splanchnic vascular bed. In this study, splanchnic vascular vasoconstriction by exogenous TxA_2 was potentiated by endogenous prostanoid inhibition by indomethacin (10 mg/kg intravenously inhibits endogenous vasodilators PGI_2 and prostaglandin E_2).[28] This finding suggested that splanchnic vasodilator eicosanoids are an important compensatory mechanism in the maintenance of blood flow.

Prostacyclin has been shown to be one of the factors that contributes to maintaining splanchnic blood flow after acute hemorrhage/reperfusion injury in the rat.[3,4] In these studies, acute hemorrhage alone caused a compensatory threefold increase in endogenous splanchnic PGI_2 release. Reperfusion of the shed blood abolished this increase in splanchnic PGI_2 and concomitantly caused a profound decrease in superior mesenteric blood flow. Both the decrease in splanchnic PGI_2 release and blood flow after hemorrhage/reperfusion injury was shown to be mediated by oxygen-derived free radicals because both injuries could be reversed by use of oxygen-derived free radical scavengers.[4-8] The increased release of splanchnic PGI_2 after acute hemorrhage subsequently was shown to be due to new synthesis of cyclooxygenase and prostacyclin synthase, which were located in the intestinal muscularis/serosa, and the new synthesis of prostacyclin synthase located in SMA.[15] These studies have focused on the events regulating SMA blood flow during acute hemorrhage/reperfusion injury. The current study examines a different pathophysiologic clinical scenario, use of endotoxin challenge as a second injury model after resuscitation of acute hemorrhage/reperfusion injury with 10 days of TPN.

The current study shows that long-term maintenance of rats on TPN for 10 days did not alter splanchnic eicosanoid release or the ratio of SMA/aortic blood flow. Subjecting the sham animals to an *E. coli* endotoxin challenge after 10 days of TPN also did not alter splanchnic eicosanoid release or *in vivo* blood flow. In contrast to these findings, subjecting the rats to an initial mild hemorrhage/reperfusion injury predisposed the animals to a marked decrease in endogenous splanchnic PGI_2 release and *in vivo* blood flow after 10 days of TPN followed by intraperitoneal endotoxin used as second injury. These experimental findings are the first to demonstrate the effect of delayed endotoxin challenge used as a second injury model after initial hemorrhage/reperfusion on splanchnic eicosanoid release and blood flow and therefore, no other literature is available with which to compare these results. However, these striking experimental results may provide new insight into one of the factors that may contribute to the initiation and evolution of the syndrome of multiple-organ failure (MOF).

The initiating factor of MOF frequently is an episode of acute hemorrhage with resulting visceral ischemia (splanchnic, renal, etc.). The initial hemorrhage usually is followed by successful fluid resuscitation and then 4 to 7 days later, the onset of MOF. Once established, MOF has profound secondary effects on splanchnic visceral function that could result in continued ileus and breakdown of the mucosal barrier to bacteria. The resulting systemic release of bacteria or bacterial products could then contribute to continuing splanchnic visceral dysfunction and dysfunction of the kidneys, lungs, liver, and heart. One must caution against extrapolating experimental findings in the rat to the human syndrome of MOF. However, these experimental findings suggest that the derangement of the splanchnic circulation after the initial hemorrhagic insult and could be an important contributing factor in the initiation and development of the ileus and enteric sepsis described during MOF.

Thus, *E. coli* endotoxin given after long-term maintenance with TPN did not alter endogenous splanchnic eicosanoid release or blood flow in the sham animals, whereas prior exposure to a mild hemorrhage/reperfusion injury predisposed the animals to decreased splanchnic endogenous PGI_2 release and to decreased SMA blood flow. These data suggest that hemorrhage/reperfusion injury predisposes the splanchnic bed from rats sustained with long-term TPN to both decreased release of endogenous PGI_2 and SMA blood flow when subsequently challenged with a second injury of endotoxin.

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